

PATENT COOPERATION TREATY

Mmu/DR/OFV

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

PFIZER RESEARCH AND DEVELOPMENT
Attn. Wood, David J.
Ramsgate Road
Sandwich
Kent CT13 9NJ
UNITED KINGDOM

EUROPEAN PHARMA
PATENT DEPARTMENT

16 MAY 2005

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

| | | |
|--|--|--|
| Date of mailing (day/month/year) | | 17/05/2005 |
| Applicant's or agent's file reference PC25833A | | FOR FURTHER ACTION See paragraphs 1 and 4 below |
| International application No. PCT/IB2005/000221 | | International filing date (day/month/year) 26/01/2005 |
| Applicant PFIZER PRODUCTS INC. | | 2/10/05 ✓ 2/12/05 ✓ W |

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46).

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Josef Ullrich

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|--|--|
| Applicant's or agent's file reference PC25833A | FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below. | |
| International application No. PCT/IB2005/000221 | International filing date (day/month/year) 26/01/2005 | (Earliest) Priority Date (day/month/year) 02/02/2004 |
| Applicant PFIZER PRODUCTS INC. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/000221

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D453/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | WO 97/03984 A (PFIZER INC; TICKNER, DEREK, L; MELTZ, MORGAN) 6 February 1997 (1997-02-06) page 8, line 5; claims 1,6 page 8 - page 9 | 1-10 |
| A | US 6 222 038 B1 (ITO FUMITAKA ET AL) 24 April 2001 (2001-04-24) cited in the application column 5, line 6 - column 6, line 64; example 1 column 7, last paragraph | 1-10 |

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

4 May 2005

Date of mailing of the international search report

17/05/2005

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Härtinger, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2005/000221

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | WARAWA E J ET AL: "Quinuclidine chemistry. 4. Diuretic properties of cis-3-amino-2-benzhydrylquinuclidine." JOURNAL OF MEDICINAL CHEMISTRY. JUN 1975, vol. 18, no. 6, June 1975 (1975-06), pages 587-593, XP002327149 ISSN: 0022-2623 Scheme 1 page 587 | 1-10 |
| A | ----- US 6 255 320 B1 (QUALLICH GEORGE JOSEPH ET AL) 3 July 2001 (2001-07-03) cited in the application claims 1,8 | 9 |
| P,A | ----- WO 2004/035575 A (PFIZER PRODUCTS, INC; DSM PHARMACEUTICALS, INC; NUGENT, THOMAS, C; SE) 29 April 2004 (2004-04-29) cited in the application page 3, last paragraph; examples page 3, line 1 - line 4 ----- | 1-10 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2005/000221

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|----------------------------|
| WO 9703984 | A | 06-02-1997 | AT 250600 T 15-10-2003 |
| | | | AU 697553 B2 08-10-1998 |
| | | | AU 6134896 A 18-02-1997 |
| | | | CA 2227194 A1 06-02-1997 |
| | | | CN 1190970 A ,C 19-08-1998 |
| | | | CZ 9800150 A3 17-02-1999 |
| | | | DE 69630123 D1 30-10-2003 |
| | | | DE 69630123 T2 08-04-2004 |
| | | | DK 840735 T3 09-02-2004 |
| | | | EP 0840735 A1 13-05-1998 |
| | | | ES 2205039 T3 01-05-2004 |
| | | | HK 1010195 A1 16-11-2001 |
| | | | HU 9900238 A2 28-05-1999 |
| | | | WO 9703984 A1 06-02-1997 |
| | | | JP 3043074 B2 22-05-2000 |
| | | | JP 10511102 T 27-10-1998 |
| | | | NO 980211 A 16-03-1998 |
| | | | NZ 310539 A 25-11-1998 |
| | | | PL 324610 A1 08-06-1998 |
| | | | PT 840735 T 27-02-2004 |
| | | | RU 2136681 C1 10-09-1999 |
| | | | US 6008357 A 28-12-1999 |
| | | | ZA 9606026 A 16-01-1998 |
| US 6222038 | B1 | 24-04-2001 | AP 299 A 14-01-1994 |
| | | | AT 135006 T 15-03-1996 |
| | | | AU 657552 B2 16-03-1995 |
| | | | AU 1990192 A 08-01-1993 |
| | | | BG 61694 B1 31-03-1998 |
| | | | BG 98248 A 15-07-1994 |
| | | | BR 9206073 A 06-12-1994 |
| | | | CA 2102179 A1 01-12-1992 |
| | | | CN 1067428 A ,C 30-12-1992 |
| | | | CZ 9203906 A3 16-02-1994 |
| | | | DE 9290063 U1 24-02-1994 |
| | | | DE 69208877 D1 11-04-1996 |
| | | | DE 69208877 T2 25-07-1996 |
| | | | DK 587723 T3 01-04-1996 |
| | | | EG 19944 A 27-02-1997 |
| | | | EP 0587723 A1 23-03-1994 |
| | | | ES 2084361 T3 01-05-1996 |
| | | | FI 935297 A 29-11-1993 |
| | | | GR 3019687 T3 31-07-1996 |
| | | | HU 70151 A2 28-09-1995 |
| | | | IE 921729 A1 02-12-1992 |
| | | | IL 102008 A 08-12-1995 |
| | | | JP 2645225 B2 25-08-1997 |
| | | | JP 7285965 A 31-10-1995 |
| | | | JP 7033386 B 12-04-1995 |
| | | | JP 6504292 T 19-05-1994 |
| | | | KR 214905 B1 02-08-1999 |
| | | | MA 22539 A1 31-12-1992 |
| | | | MX 9202554 A1 01-11-1992 |
| | | | NO 934312 A 29-11-1993 |
| | | | NZ 242956 A 27-06-1995 |
| | | | NZ 270673 A 27-07-1997 |
| | | | OA 9867 A 15-08-1994 |
| | | | PL 171379 B1 30-04-1997 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2005/000221

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|----|---------------------|--|--|
| US 6222038 | B1 | | PT 100546 A ,B RO 110499 B1 RU 2103269 C1 SK 390692 A3 WO 9221677 A1 US 5807867 A US 5939433 A ZA 9203942 A | 31-08-1993 30-01-1996 27-01-1998 04-02-1998 10-12-1992 15-09-1998 17-08-1999 29-11-1993 |
| US 6255320 | B1 | 03-07-2001 | AT 244239 T AU 767334 B2 AU 4424800 A BG 106204 A BR 0011094 A CA 2372238 A1 CN 1353711 A ,C CZ 20014269 A3 DE 60003679 D1 DE 60003679 T2 DK 1181290 T3 EA 3731 B1 EE 200100656 A EP 1181290 A1 ES 2199825 T3 HK 1046284 A1 HR 20010904 A1 HU 0201301 A2 WO 0073304 A1 JP 2003501354 T MX PA01012325 A NO 20015848 A NZ 515349 A PL 352716 A1 PT 1181290 T SI 1181290 T1 SK 17332001 A3 TR 200103473 T2 ZA 200109775 A | 15-07-2003 06-11-2003 18-12-2000 31-07-2002 19-03-2002 07-12-2000 12-06-2002 17-04-2002 07-08-2003 27-05-2004 29-09-2003 28-08-2003 17-02-2003 27-02-2002 01-03-2004 08-02-2005 28-02-2003 28-08-2002 07-12-2000 14-01-2003 22-07-2002 18-12-2001 26-03-2004 08-09-2003 30-09-2003 31-12-2003 02-07-2002 22-04-2002 28-11-2002 |
| WO 2004035575 | A | 29-04-2004 | AU 2003277353 A1 WO 2004035575 A1 US 2004116704 A1 | 04-05-2004 29-04-2004 17-06-2004 |

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/B2005/000221

International filing date (day/month/year)
26.01.2005

Priority date (day/month/year)
02.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D453/02

Applicant
PFIZER PRODUCTS INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Härtinger, S

Telephone No. +49 89 2399-8289



107/08049

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2005/000221

30.04.05

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/B2005/000221

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|-------------------------------|-------------|------|
| Novelty (N) | Yes: Claims | 1-10 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-10 |
| | No: Claims | |
| Industrial applicability (IA) | Yes: Claims | 1-10 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2005/000221

Re Item V:

1. The application relates to a process for preparing camphersulfonic acid (CSA) salt of 1-(2S,3S)-2-Benzhydryl-N-(5-ter-butyl-2-methoxybenzyl)quinuclidin-3-amine having the formula Ib. The process makes use of intermediates in the CSA salt form, of which the preferred intermediate Via is likewise claimed.

The relevant prior art is represented by the following documents.

- D1: WO 97/03984 A (PFIZER INC; TICKNER, DEREK, L; MELTZ, MORGAN) 6 February 1997 (1997-02-06)
- D2: US-B1-6 222 038 (ITO FUMITAKA ET AL) 24 April 2001 (2001-04-24)
- D3: WARAWA E J ET AL: "Quinuclidine chemistry. 4. Diuretic properties of cis-3-amino-2-benzhydrylquinuclidine." JOURNAL OF MEDICINAL CHEMISTRY. JUN 1975, vol. 18, no. 6, June 1975 (1975-06), pages 587-593, XP002327149 ISSN: 0022-2623
- D4: US-B1-6 255 320 (QUALLICH GEORGE JOSEPH ET AL) 3 July 2001 (2001-07-03)

The cited prior art makes use of CSA in catalytic amounts to achieve the amination of 3-ketoquinuclidine. CSA has also been used for the resolution of racemic end-products. While enantiomerically pure cis-intermediates of the type presently used are known in the art, none of the cited documents discloses CSA quinuclidine salts, which were pulled through a multi-step synthesis procedure. By consequence, the claimed processes and intermediate (VIa) appear to be novel in the sense of Art. 33(2) PCT.

The most pertinent prior art is represented by D1, D2 and D3. D1 teaches the use of CSA for the resolution of racemic 2-Benzhydryl-N-(5-iso-propyl-2-methoxybenzyl)quinuclidin-3-amine. The said resolution step only occurs at the end of the multi-step procedure and does not involve the transformation of CSA intermediates. While the use of enantiomeric intermediates, such as 2-Benzhydryl-N-benzyl)quinuclidin-3-amine and 2-Benzhydryl-quinuclidin-3-amine, are suggested for the production of 2S,3S-cis end products (eg. page 8 of D1), the use of intermediates in salt form is not taught. Similarly, the documents D2 and D3 teach, that

enantiomerically pure cis-intermediates may be pulled through analogous multi-step procedures, whereby the enantiomers have been obtained by chromatography or by formation with chiral acids at the final synthesis step. The skilled person, who was looking to find an alternative process for the synthesis of known product (I), was therefore left without guidance, when solving the problem by the use of the present CSA quinuclidine intermediates (VIa) and (VII). The claimed processes and the intermediates, which are essential for proposed solution, are therefore considered to be the result of not obvious modifications of the prior art. The claimed subject-matter appears therefore to meet the requirement of Art. 33(3) PCT.

Re Item VI:

1. The international patent application D5 (= WO 2004/035575 A, PFIZER PRODOUCTS, INC; DSM PHARMACEUTICALS, INC; NUGENT, THOMAS, C; SE, 2004-04-29) has been published between the priority and filing date of the present application. The free amino intermediates and the CSA salt of final products disclosed therein do therefore not form part of the state of the art as defined in the PCT. By consequence, D5 has been disregarded from further considerations.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ BLACK BORDERS

☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☒ FADED TEXT OR DRAWING

☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☒ GRAY SCALE DOCUMENTS

☒ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.